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INDUSTRIAL GUMS

Polysaccharides and Their Derivatives

THIRD EDITION

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Soc. Symp. Ser., 45, 90
Mueller, D. J. Stancioff,
. Biol., 90, 253 (1974).
Carbohyd. Res., 182, 1
) (1970).
'iscuss. Chem. Soc., 57,
rkin Trans., 11, 1608
. 153 (1972).
J. Chem. Soc., Chem.
Sapporo, Japan, 451
46 (1971).
nd D. A. Rees, J. Mol.
. 10, 243 (1971).
Food Nutr. Sci., 6, 45
.4, 292 (1968).
ure, 222, 687 (1969).
., J. Agr. Chem. Soc.
)80).
47, 1063 (1969).
i3 (1965).
:hnol., 6, 239 (1972).
:mun., 805 (1969).
983).

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CHAPTER 3

CHEMICAL MODIFICATION OF GUMS

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INTRODUCTION

Natural polysaccharides are frequently modified with chemicals to give them new properties for broader application. Sometimes the modification can be made in steps, giving a range of new products having properties quite different from the parent material. In many instances, the modification can produce a very specific effect because of the novel properties of the new structure. It is, at times, possible to give one polysaccharide the properties of another polysaccharide, allowing the replacement of a high-priced gum with a lower-priced modified gum.

Such chemistry is fairly well established, but unfortunately for the specialized food research or process chemist, information is scattered in the starch[1] and cellulose[2] literature and in descriptions of other polysaccharides. This chapter presents a variety of commercial methods for the modification of polysaccharides. It is not intended to provide a description of all modification techniques or research methods but rather to

describe a selection of useful reactions that may give food chemists and others an indication of possibilities. Details of procedures can be obtained through the references.

Polysaccharides occurring in nature are all highly hydroxylated, usually with three hydroxyl groups for each chain unit. These hydroxyl groups, in conjunction with the ring and glycosidic oxygen atoms, provide five loci on average for hydrogen bonding on each chain unit. Consequently, polysaccharides are very hydrophilic and tend to bind water tenaciously. In fact, the initial binding energy for water to a polysaccharide is as strong as that to the chemical drying agent phosphorous pentoxide. A normally dry polysaccharide under ambient conditions of 25°C and 60–80% relative humidity will contain 8–12% water. Therefore, the polysaccharide would normally be highly hydrated in a water dispersion and would completely dissolve to produce a monodisperse solution. Despite the tendency to completely surround themselves with an "atmosphere" of bound water thereby becoming fully solvated and dissolved, many polysaccharides are prevented from dissolution because of mutual intermolecular bonding. This intermolecular association occurs mainly through hydrogen bonding, which often results in multiple sturdy junction zones or crystalline areas. Crystallization is made possible by the long regions of structured regularity that are inherent in most polysaccharides. This allows chains to fit into such hydrogen bond stabilized regions despite destabilizing effects such as thermal action and conformational irregularities. Insolubility probably does not require a great deal of crystallinity, and, indeed, the most accurate representation would probably entail a network of crystalline and amorphous, spaghetti-like regions. Examples of polysaccharides in which this strong junction zone formation persists are cellulose, the mannans of ivory nut, and starch amylose, all which tend to be insoluble under normal conditions.

It follows that if such polysaccharides can be prevented from forming junction zones, as would be the case if they contained branches or charged groups, thereby preventing association through steric hinderance or coulombic repulsion, then solubility should result. This is indeed the case as has been amply demonstrated upon preparation of the many useful water-soluble derivatives of cellulose and starch. In such materials, short chain ethers and esters as well as charged carboxyalkyl and aminoalkyl moieties are added to the polysaccharides to give water-soluble materials with a variety of unique and useful properties.

It is surprising how extensively the properties of a neutral polysaccharide can be changed by introducing a small degree of derivatization. As an example, adding as little as one acetyl per every 100 glucosyls to

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starch, a degree of substitution (DS) of 0.01, improves freeze–thaw stability markedly, and cellulose is converted to a soluble, highly viscous and therefore very useful gum by the introduction of as little as 3 carboxymethyl groups per every 10 glucosyl units. Polysaccharides with side chain branches or with charged groups that tend to be already soluble are usually less altered through derivatization. Cases in which derivatives of such materials have proven commercially viable usually provide a specific effect, as, for example, in improving protein binding or surface activity.

The crystallinity occurring naturally in most linear, insoluble polysaccharides tends to make derivatization difficult. In order to effect a uniform substitution it is necessary to first disrupt crystalline zones, thus exposing hydroxyls for reaction. This is usually accomplished by using nonreactive protic solvents, which compete well for hydrogen bonding sites and gradually disrupt crystalline areas, or by using aqueous alkali. Strong aqueous alkali is used almost entirely by industry in preparing derivatives. Steeping a polysaccharide in this material causes rapid swelling and near solubilization, at which point the addition of appropriate alkylating agents, such as alkyl halides or alkyl oxides, results in derivatization, usually at surprisingly high efficiencies.

As noted earlier, on average, three hydroxyls per anhydro sugar unit are available for substitution. The relative reactivity of these varies considerably, however, due both to accessibility within crystalline/amorphous regions and to positional effects. Even in a fully solvated condition, the hydroxyl groups show different reaction rates as influenced by a number of factors, including inductive effects as well as steric effects and conformation. In cellulose and starch, the most reactive hydroxyl group is at *C*-2. For example, in mercerized cotton[2] OH-2 is about 30% more reactive than either OH-3 or OH-6. Reactive rates can be altered, however, by reaction conditions. When starch is methylated to high DS with dimethyl sulfate in a strong sodium hydroxide solution, the substitution ratio at *C*-2 to *C*-3 to *C*-6 is 6 : 1 : 7,[3] whereas methylation in more dilute alkali to a DS of only 0.6 gives a *C*-2 to *C*-3 to *C*-6 ratio of 10 : 1 : 4.[4] Alkali strength also plays a significant role in determining properties of the final product. Thus, carboxymethyl celluloses prepared from the same starting cellulose and substituted to the same level but varying with respect to alkali concentration or time during initial swelling may have different solution properties. This difference is attributed to differences in the substitution pattern as affected by the relative amounts of crystalline versus amorphous regions available during reaction; hydroxyls in amorphous regions react at faster rate. Blockwise substitution patterns tend to give a more structured, pituitous flow

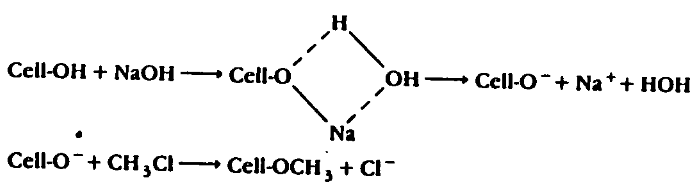
character, whereas a random substitution reflect a smoother flow behavior.

A vast array of derivatives based almost exclusively on starch and cellulose are currently available, many of which are approved for food use. Use of guar as a starting material for derivatization is also increasing but use of many of the other gums as starting materials, while reported in the literature, is precluded because of a higher price or lack of sufficient performance benefit to warrant their manufacture. The following sections discuss some of the more commercially important types of polysaccharide derivatives in terms of manufacture, properties, and markets. A more in-depth treatment of specific types is presented in subsequent chapters.

Ethers

Common industrial ethers are methyl, ethyl, hydroxyethyl, hydroxypropyl, carboxymethyl, and aminoethyl. Mixed ethers are also available and offer a range of properties as influenced by relative substitution levels as well as order of addition. Commercially important examples of this are the methylhydroxypropylcelluloses.

Methylcellulose (Chapter 18) was first prepared in 1905.[7] Early methods of preparing this ether involved steeping of cellulose in 40–50% sodium hydroxide, followed by reaction with dimethyl sulfate. Modern commercial methods are based on reaction of the alkali cellulose with methyl chloride in organic solvents at a much higher solids level in batch or continuous systems to a lower production costs.[6–8] Reaction chemistry follows the familiar Williamson ether synthesis as shown.

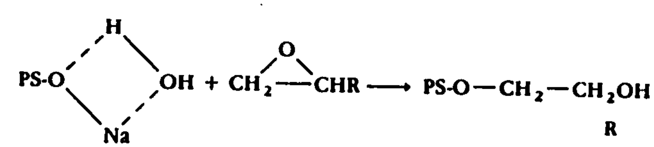


Commercial methylcelluloses are substituted to a DS range of 1.5–2.0 and are soluble in water and insoluble in organic solvents. Better organic solubility can be attained through substituting ethyl for methyl and going to higher DS levels. Solutions of methylcellulose and methylstarch tend to undergo thermoreversible gelation when heated. Gelation is attributed to the formation of a crystalline network of tri-*O*-methyl-D-glucopyranosyl units.[9] Methyl and ethylstarch are prepared in much the same way as their cellulose counterparts, except that starch granules are first treated with a small amount of mineral acid and heated to 100°C,

then alkali and methyl chloride are added. An alternative method is to mix starch with pulverized sodium hydroxide and methyl chloride and then holding it for 12 hr at 32°C.[10]

Another type of ether substituent, the carboxymethyl group, has been substituted successfully on a number of types of polysaccharides, the most widely used of which is carboxymethylcellulose. Production of this one derivative alone in the United States is now estimated to exceed 40,000 metric tons annually. Its preparation was first patented in 1918[11] and, although commercial production methods have improved somewhat since then, it is still prepared using basically the same chemistry and reaction conditions. Again, Williamson ether synthesis chemistry is used but with sodium chloroacetate as a reactant instead of alkyl halide. Substitution predominates nearly equally between the *C*-2 and *C*-6 positions, with a small amount of substitution at *C*-3.[12] While it is possible to prepare low-DS products under aqueous conditions, most processes rely on the use of aqueous mixtures of alcohols and ketones to achieve the 0.4–1.2 DS ranges needed for commercial, water-soluble materials. Lower cost, lower DS materials for use in laundry detergents as a soil antiredeposition aid are prepared by simply moistening cellulose with sodium hydroxide solution and warming with sodium chloroacetate.

Hydroxyalkyl-substituted gums represent the largest group of polysaccharide ether derivatives. They are almost all made by attack of the poly-anion on an oxirane ring to produce the corresponding hydroxyalkyl derivative (as shown).



A number of important hydroxyalkyl derivatives of cellulose (Chapter 19) are made in this manner, including hydroxyethyl and hydroxypropyl cellulose.[13]

Unlike the alkyl and carboxymethyl derivatives, substitution of hydroxyalkyl does not decrease the number of hydroxyls but instead provides a new hydroxyl site, which is primary and sterically less hindered than the hydroxyl replaced. Thus, after one oxirane has reacted to form the hydroxyalkyl substituent, its hydroxyl group can react with another oxirane to extend the side chain another unit. In commercial hydroxyethylcellulose it is common to find a DS of 0.8 to 1.8 and an MS (molar substitution) of 1.8 to 3.5 (see Chapters 18 and 19), indicating that a number of hydroxyethyl substituents have reacted further to give

at least short side chains of poly(ethylene oxide). Another derivative sharing this effect is hydroxypropylcellulose. Commercial materials normally manufactured to a DS level of 2.2 to 2.8 have been found to contain an MS of hydroxypropyl substituents of 3.5 to 4.5.

Starch processing and use has also benefitted greatly through the development of methods of adding hydroxyalkyl substituents. In contrast to cellulosic materials, in which relatively high levels of substitution are required to effect solubilization, very little add-on is needed to give desired changes in properties. Usually substitution is achieved without disruption of the starch granule. Cold-water-insoluble hydroxyalkyl ethers of starch (Chapter 21), with an average of up to 0.1 mole of alkyl group per D-glucopyranosyl unit, are prepared by reacting starch in a water suspension with ethylene oxide or propylene oxide; this occurs without appreciable alteration of granule structure. The product is easily dewatered and washed to a high degree of purity. One process involves reacting ethylene oxide with a 35–40% suspension of starch in a dilute sodium hydroxide solution at a temperature below the swelling temperature of the starch.[14,15] The swelling may be further controlled by adding soluble alkali metal salts to the reaction mixture.[16] Both sodium chloride and sodium sulfate have been used effectively, making it possible to easily prepare starch ethers of up to DS 0.1 commercially. Higher levels of incorporation are possible through the use of higher levels of alkali, salt, and oxide, but processing problems arise as the product tends to gelatinize during washing of the filter cake.

Substitution in starch to an average of 0.05–0.10 of a hydroxyalkyl per D-glucopyranosyl unit results in a drastic alteration of paste and film properties. The gelatinization temperature is lowered significantly, often by as much as 18°, and thus starch granules readily disintegrate when heated in water. On cooling, the hydrosols form translucent, very cohesive pastes that exhibit good stability and can be stored for long periods if properly preserved. Furthermore, these hydrosols when cast and dried produce flexible, nontacky films. Such low DS starch hydroxyalkyl ethers are used extensively in paper and textiles as adhesives and coatings. As a paper coating, the excellent film properties of the material are effective in increasing resistance to penetration of hydrophobic materials such as greases, waxes, varnishes, and inks. The high adhesive strength of the materials also improves coating pick values and ink receptivity and improves printing properties. In the textile industry, low DS hydroxyalkyl starches are used extensively in warp sizing because of improved rate of hydration, reduced gelling tendency, compatibility with sizing adjuncts, ease of desizing, and excellent film characteristics.

Hydroxypropyl ethers of both cellulose and starch are cleared for use in foods as direct additives. Hydroxypropylcellulose (Chapter XX) is

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effective as a whipping aid and emulsifying agent and is used in whipped toppings. Hydroxypropyl starches are used in foods that require a clear or translucent thickener with improved freeze–thaw stability. These starches are often produced with a slight amount of crosslinking to control texture and to help prevent irreversible thinning caused by high temperature and shear, and to improve acid stability during processing.

In addition to the cellulose and starch ethers, similar derivatives of guar have found more recent commercial use and deserve mention. Guar (Chapter XX) is easily substituted under aqueous conditions in the presence of a mild alkali, with various alkylating agents for starch and cellulose as described above. While a reaction can be carried out using guar powder, it is often advantageous to react guar splits with reagent in a sealed reactor. This is followed by washing to remove alkali and by-products, and then drying and grinding. Borate salts, which crosslink the galactomannan and inhibit swelling during reaction, may also be added to facilitate processing. Using such techniques, a number of guar ethers, including hydroxyethyl, hydroxypropyl, and carboxymethyl adducts as well as several mixed types, are prepared commercially.[17] Carboxymethyl guar can compete with carboxymethylcellulose for use in drilling muds, while hydroxyalkyl guars are used in enhanced oil recovery, paper, textiles, and cosmetics. Mixed ethers of guar are also increasingly being used commercially. Carboxymethylhydroxypropyl guar produced by sequential addition of the two substituents is used in oil recovery and other applications because of its improved compatibility with organic solvents and improved crosslinking with multivalent cations. Another derivative, the 2-hydroxypropyltrimethylamino adduct, which is produced using similar addition chemistry is manufactured for use in shampoos and bar soaps.

Carboxymethyl and hydroxyalkyl derivatives of locust bean gum and a number of other gums, including algin,[18] xanthan,[19,20] and other biosynthetic gums, have been reported. While useful improvements or modifications to properties are often seen, the cost of modification added to the already premium price of such gums makes development unlikely. In cases where improvements or modifications to properties suggest possible food use, the cost of testing plus considerable time involved must be weighed against expected usage, returns, and risk.

Another common type of etherification reaction is reverse Michael addition,[21] involving the alkali-catalyzed addition of an activated vinyl group. One of the best known examples is the reaction of acrylonitrile with polysaccharides to yield the O-(2-cyanoethyl) derivative as shown.

$$\text{PS-O}^- + CH_2{=}CH{-}C{\equiv}N + HOH \rightleftharpoons \text{PS-O}{-}CH_2CH_2{-}C{\equiv}N + OH^-$$

Starch can be substituted in this manner to DS levels approaching 3.0.

Depending on reaction conditions, highly water insoluble products are produced that withstand steam sterilization conditions well and are resistant to breakdown by microorganisms.[22] Even though the above reaction is reversible under basic conditions, it is possible, under suitable conditions, to hydrolyze a part of the cyanoethyl groups to carboxyethyl, thereby providing an alternate route to production of the familiar carboxyalkyl ether.

Esters

Polysaccharides are polyols and hence readily form esters with a variety of esterifying reagents. Commercial esters are formed traditionally by reaction with acids and acid anhydrides. However, in the laboratory, esters such as acetate may be prepared using several other reagents, such as ketene and vinyl acetate.

Some of the earliest commercial polysaccharide esters were the acetates of cellulose, which were used to make plastics and fibers. These were manufactured by treating cotton linters or wood pulp with acetic anhydride, using glacial acidic acid as a solvent and sulfuric acid as a catalyst.[23] The full triacetate is not formed by this treatment but can be obtained by retreating the partial ester with the same reagents, except that the catalyst used is a very small amount of perchloric acid. In the laboratory, triacetates of polysaccharides are easily prepared by reaction with acetic acid in pyridine at 100°C for 4 hr.[21,24]

Commercial starch acetates (Chapter 21) normally have a DS of 0.01 to 0.2 and are prepared with the granule structure intact. One major purpose of derivatization is to improve the formation and stability of colloid dispersions. Freeze–thaw stability is also conferred by lessening the tendency toward molecular association or retrogradation. Low DS starch acetates are normally prepared by the addition of acetic anhydride in an aqueous slurry at pH 7–11. Esterification efficiency under these conditions is around 70%.

A number of inorganic esters are made commercially. The earliest was cellulose nitrate, prepared by treating cotton linters or wood pulp with a mixture of nitric and sulfuric acid. Under forcing conditions, the trinitrate is formed, which is the powerful explosive, guncotton. Products of around DS 2.5 were used in making early movie film and fabrics which were, of course, very flammable.

Phosphate esters are used extensively in the manufacture of various commercial modified starches. As such, they are normally incorporated at low levels of around DS 0.2 to 0.4. Even at these low levels, however, they induce large changes in the properties of starch through introduction of charges and through steric effects and crosslinking. Phosphate groups are easily introduced by heating starch powder, previously sprayed with a solution of sodium tripolyphosphate, to 100–160°.[25] The resulting starch phosphate monoester product dissolves readily in water to give highly viscous solutions, which show improved clarity and stability. The gelatinization temperature is gradually lowered as DS is raised until, at a DS of about 0.07, products soluble in cold water are obtained.

Starch phosphate diesters are also easily formed by reacting starch with sodium trimetaphosphate in the dry state, following a procedure similar to that just described, or by reacting starch in slurry with phosphoryl trichloride or phosphorus oxychloride. Either of these reactions can give an intramolecular reaction wherein two hydroxyls of one molecule are esterified, but which reaction usually leads to intermolecular crosslinking. This type of modification leads to significantly altered properties, which are discussed later under the section on crosslinks.

Sulfate ester groups are also easily introduced and usually result in marked physical properties change. These derivatives have been studied extensively for a possible heparin replacement and for products using the naturally sulfated seaweed galactans such as carrageenan. This includes many dairy products, such as ice cream, flavored milk drinks, and dessert gels, where the polysaccharide sulfates' effectiveness at very a low concentration is believed to be attributable to a strong interaction with milk proteins.

While polysaccharides may be sulfated by direct treatment with sulfuric acid, facile sulfation is achieved through treatment with complexes of fuming sulfuric acid and weak organic bases such as pyridine, dimethylsulfoxide, and dimethylformamide[26,27] at lowered temperature. In this manner, high DS levels are obtained with little damage to the polysaccharide backbone. Starch, cellulose, galactomannans, and other polysaccharides are generally substituted to over DS 2 using such complexes to give water-soluble, viscous products with high affinity for metal ions, proteins, and other positively charged materials.

Grafts

Grafting a synthetic polymer to a natural polysaccharide is a way of creating large molecules that have some of the characteristics of each individual polymer. A large amount of work has been done by investigators at the Northern Regional Research Center, U.S. Department of Agriculture, Peoria, Illinois.[28] Work has been extensively directed toward water absorbants[29,30] and biodegradable polymers that can be cast into sheets. While in theory any polysaccharide can be recipient of grafts, starch (Chapter 21) has been most investigated because of its availability in large quantity at low cost.

Grafting is initiated by generating one or more free radicals on the polysaccharide chain and allowing these radicals to react with polymerizable monomers that will constitute the grafted chain. Thus, if a polysaccharide is reacted, for example, with high energy radiation, such as X-rays, ultraviolet radiation, or beta-radiation, free radicals may be created in various ways but principally through hydrogen atom elimination. More often, a free radical generator such as ferrous ion or ceric ammonium nitrate, along with hydrogen peroxide, is used.[31-33] After formation, the free radical is available to initiate a free-radical polymerization as illustrated by the following pathway for reaction of starch with acrylonitrile.

$$\text{Starch-OH} \longrightarrow \text{Starch-O}\cdot + CH_2{=}CH(CN) \longrightarrow \text{Starch-O}{-}CH_2{-}\dot{C}H(CN)$$

$$\text{Starch-O}{-}CH_2{-}\dot{C}H(CN) + CH_2{=}CH(CN) \longrightarrow \text{Starch-O}{-}CH_2{-}CH\begin{cases} \dot{C}N \\ CH_2CH(CN) \end{cases}$$

Although not all radicals produced on a polysaccharide chain react with monomer to initiate growth of a synthetic polymer chain, efficiencies can be fairly high, often exceeding 50%. Many different monomers subject to free radical polymerization have been tried successfully, with those commonly used being vinyl acetate, acrylamide, and methyl methacrylate.

Oxidations

Oxidation is not used to a significant extent for modification of industrial polysaccharides, although it has great potential if the reactions can be made more specific. Present oxidation reactions, of whatever nature, are sufficiently random in their action that polymer chains usually undergo significant degradation and loss of viscosity and functionality. In fact, oxidation by hypochlorite or hydrogen peroxide has been used industrially to depolymerize polysaccharides to produce lower viscosity to enable their use in producing more manageable concentrated solutions.

Starch oxidized with hypochlorite at pH 10 was produced on a rather large scale from about 1920 to 1950 with production then diminishing to present low levels. Starch, thus treated, has improved properties in that it disperses in water at a much lower temperature, shows good clarity even at higher concentrations, and is less prone to setback or gelation. Since the oxidation with hypochlorite can be carried out as part of the normal processing, with need for very low levels of oxidant, the cost tends to be low. Along with chain cleavage, however, this treatment results in the formation of carbonyl functions that cause it to undergo extensive browning reaction with proteins and to be very unstable in the presence of even mild alkali. This instability is due to the well-known beta-elimination reaction common to any polysaccharide having carbonyl functionality at any position in the sugar ring.

Another type of oxidation which has been studied extensively and would seem to offer promise of commercial use is that of treating polysaccharides in a dry or slurry state with nitrogen tetroxide, N_2O_4.[34,35] This reaction is specific in that primary hydroxyls are oxidized to carboxylic acid groups, thus offering a low-cost means of producing a polyuronan. Applied to cellulose, a new polysaccharide having some of the physical characteristics of carboxymethylcellulose can be envisioned. In practice, however, it is found that as with oxidation with hypochorite, a small amount of oxidation occurs at other sites, thus rendering these products susceptible to alkaline-catalysed beta-elimination as well, an unacceptable drawback in that such products would be sold primarily as viscosifying agents.

Crosslinks

The introduction of crosslinks between adjacent chains in polymer solutions has always existed as a very important and useful means of properties modification. Such crosslinks range from the weak noncovalent type represented by hydrogen bonds and salt type bridging seen between calcium ions and carboxyl groups to strong covalent bonds of type represented by diethers and diesters. While weak crosslinks are of great interest in explaining many of the phenomena seen in polymer solutions and gels, we are here mainly concerned with introducing permanent crosslinks which can be introduced into a product such that, upon hydration, a modification or improvement in properties results and persists through sometimes harsh processing conditions.

As mentioned previously, phosphate diester groups introduced through the use of trimetaphosphate, phosphoryl trichloride or similar reagents are important means of introducing such a crosslink, which tends to be stable under most conditions, particularly those encountered in neutral to slightly acid foods. Again, as would be expected, most of the work and commercial success using such crosslinks has been in the starch area but similar modification of other polysaccharides is possible. Generally, in starch chemistry, crosslinking with phosphate diester gives significant properties improvements important to both food

and nonfood uses alike, including increased viscosity, improved gelation, and improved texture.

Crosslinked starches are used in foods when a stable, high viscosity paste is needed, particularly if dispersions are to be exposed to high shear, high temperature, low pH, or combinations thereof. Trends toward continuous cooking require increased shear resistance and stability during exposure to hot surfaces, an example of which would be conditions encountered during extrusion cooking. Crosslinked starches show improved storage stability and effective thickening in salad dressings in which exposure to low pH for extended shelf-life periods is common. Crosslinking, combined with certain types of drying techniques, such as drum drying, have been used to impart special properties to foods, such as pulpiness or a fatlike texture and mouthfeel. This type of product is becoming especially important in todays' reduced fat products. Already a number of proprietary starches based on some of the modifications discussed are available commercially.

Other crosslinking agents of a more general nature, which in theory could be applied to nearly any polysaccharide system, include epichlorohydrin, vinylsulfone, the diisothiocyanates, and a number of diepoxides and diolefins such as 1,2:5,6-diepoxyhexane and 1,2:5,6-hexadiene. Epichlorohydrin is a very effective crosslinker for starch granules and, at sufficiently high levels of treatment, renders the granule completely resistant to disruption even under autoclave conditions. Applied to guar, it causes the material to become insoluble at even very low levels of crosslinking. Unfortunately, this is an all-too-common problem in attempting to augment viscosity and improve properties through crosslinking in that only very few interchain links are needed to shift the balance between solubility and insolubility in sols of such high molecular weight, linear polymers. A solution to this problem might be to tie such polymers together end group to end group and, indeed, this approach has been tried a number of times by polymer chemists without success.

Again, the crosslinked starches represent the most successful use of this type of modification for industrial use. Their use in adhesives for making corrugated paper and other paper products and as thickener and rheology-control additives in dye sols in fabric and carpet printing are two important areas. They also find use in certain health care items, such as dusting powders and antiperspirants, and in a number of other diverse areas, including printing inks, textile sizing, and oil-well drilling.

Current Derivatives Market

Total consumption of gums, including starches, modified starches, and modified cellulosics, is estimated to be about 2.5 billion lb

(10^9 kg)/yr in the U.S. alone, with a market value exceeding \$1 billion. Worldwide consumption of gums is estimated to be more than double this amount. Use in foods and animal feeds accounts for some 620 million lb (2.8×10^8 kg), with a market value of about \$375 million; use in paper products consumes 1.05 billion lb (4.8×10^8 kg) or \$215 million. Other industries consuming large volumes of gums include textiles, petroleum, paints, and cosmetics at poundage share levels of generally 1% or less but at 3–5% of dollar share, owing to the tendency for these industries to consume the higher price/performance gums.

Starch has the largest market share of the modified gums. Out of a 1990 U.S. starch market estimated at 8 billion lb (3.6×10^9 kg), about 30% or 1.6 billion lb is sold as sold as modified starches ranging from acid-hydrolysed to phosphorylated and alkylated types.

Cellulosics, which represent the largest market segment of modified polysaccharides after the starches, had a 1990 market share of 183 million lb (8.3×10^7 kg), worth about \$312 million. A breakdown by cellulose type is shown in Table 1.

Both modified starches and the cellulosics are used in a variety of products in which low to moderate pricing (starch \$0.20–50/lb) and cellulosics (\$0.75–3.00/lb) and good performance have led to high growth.

Starches, with growth tied largely to paper and foods, have shown growth rates of nearly 5% for the years 1980 to 1990. Many of the cellulosics, including carboxymethyl, methyl, and hydroxymethyl adducts also tied to these industries have also shown as good or better growth in this same time frame. Declines in oil prices in the mid 1980s tended to reverse growth trends for certain grades of HEC and CMC used in oil recovery but, in general, this has not had a lasting effect on growth.

Another polysaccharide mentioned previously as finding more and more use in derivatized form, guar, is making an impact on the deriva-

TABLE 1

Consumption and Value of Modified Cellulosic Gums, 1990

Product	Million lb	\$ Million
Carboxymethylcellulose	92.2	124.4
Hydroxyethylcellulose	47.6	95.8
Methylcellulose	25.9	54.5
Carboxymethylhydroxyethylcellulose	2.7	7.3
Hydroxypropylcellulose	1.3	3.0
Microcrystalline cellulose	13.0	27.0
Total	182.7	312.0

tives market both in new uses and, to a lesser extent, in taking some market share from the cellulosics. Hydroxypropyl guar, which was first marketed early in the 1960s by Stein-Hall (Celanese) showed steady growth to a market share of about 34 million lb in 1982, tied largely to enhanced oil recovery, then declined rapidly with falling oil prices to about 25 million lb. It has rebounded today to a market share of around 30 million lb. Carboxymethyl guar, again with growth tied to oil recovery, has experienced slow growth despite good performance and in 1990 showed a market share of about 2 million lb. Brighter performance is seen for the newer cationic guars, which are often produced as mixed ethers containing hydroxypropyl and carboxymethyl groups in addition to aminoethyl substituents. These materials, targeted for the personal care markets, including shampoos, bar soaps, and skin care items, had already reached a market level of about 4 million lb by 1990 and continue to show good growth.

References

1. "Starch: Chemistry and Technology," R. L. Whistler, J. N. BeMiller, and E. F. Paschall, eds., Academic Press, New York, 1984.
2. J. L. Bose, E. J. Roberts, and S. P. Roland, *J. Appl. Polymer Sci.*, **15**, 2999 (1971).
3. S. A. Fydholm, "Pulping Process," Interscience Publishers, New York, 1967, p. 149.
4. G. Ezra and A. Zilka, *J. Macromol. Sci., Chem.*, **3**, 1589 (1969).
5. W. Suida, *Monatsh. Chem.*, **26**, 413 (1905).
6. R. W. Swinehart and A. T. Massberg, U.S. Patent 2,331,865 (1943).
7. W. Loedige, F. Loedige, J. Luecke, and E. Lipp, Germ. Offen. 2,635,403 (1978; *Chem. Abstr.*, **88**, 122865y (1978).
8. W. Wuest, H. Leischne, W. Raehse, F. Carduck, and N. Kuehne, Germ. Offen. 2,929,011 (1981); *Chem. Abstr.*, **94**, 123415n (1981); W. Wuest, H. Leijschner, F. J. Carduck, W. Raehse, and N. Kuehne, Germ. Offen. 3,005,700 (1981); *Chem. Abstr.*, **95**, 171346h (1981).
9. J. Roots, M. Mosely, and B. Nystrom, *Chemica Scripta*, **16**, 201 (1980).
10. K. J. Gardinier and W. Hemibuerger, Germ. Patent 2,900,073 (1980).
11. E. Jansen, Germ. Patent 332,203 (1918).
12.
13. A. E. Broderick, U.S. Patent 2,682,535 (1954); *Chem. Abstr.*, **48**, 11100 (1954).
14. F. del Valle, J. V. Tuschoff, and C. E. Streaty, U.S. Patent 4,000,128 (1954).
15. C. O. Szymanski, M. M. Tessler, and H. Bell, U.S. Patents 3,804,828 (1974) and 3,857,976 (1974).
16. T. Tsuzuki, U.S. Patent 3,378,546 (1068).
17.
18. E. Nishide, *Kogyo Kagaku Zasshi*, **66**, 458 (1963); *Chem. Abstr.*, **60**, 3090 (1964).
19. R. G. Schweiger, U.S. Patent 3,236,831 (1966).
20. R. G. Schweiger, U.S. Patent 3,256, 271 (1966).
21. G. F. Touzinsky, *J. Org. Chem.*, **30**, 426 (1965).
22. Monsanto Chemical Co., Brit. Patent 808,290 (1959); *Chem. Abstr.*, **53**, 9708 (1959).

23.
24. L. J. Tange, L. B. Genung, and J. W. Mench, *Methods Carbohydr. Chem.*, **3**, 193 (1963).
25. R. W. Kerr and F. C. Cleveland, Jr., U.S. Patent 2,884,413 (1956).
26. R. L. Whistler and W. W. Spencer, *Arch. Biochem. Biophys.*, **95**, 36 (1961).
27.
28. G. F. Fanta and W. M. Doane, *in* "Modified Starches," O. B. Wurzburg, ed., CRC Press, Boca Raton, Florida, 1986, p. 149.
29. M. O. Weaver, E. B. Bagley, G. F. Fanta, and W. M. Doane, U.S. Patents 3,935,099; 3,981,100; 3,985,616; and 3,997,484 (1976).
30. M. O. Weaver, R. R. Montgomery, L. D. Miller, V. E. Sohns, G. F. Fanta, and W. M. Doane, *Staerke*, **29**, 410 (1977).
31. J. C. Arthur, Jr., *Advan. Macromol. Chem.*, **2**, 1 (1970).
32. P. W. Moore, *Rev. Pure Appl. Chem.*, **20**, 139 (1970).
33. O. Hinojosa and J. C. Arthur, *J. Polym. Sci., Part B*, **10**, 161 (1972).
34. W. O. Kenyon and C. C. Unruh, U.S. Patent 2,472,590 (1949).
35. R. W. Kerr, *J. Am. Chem. Soc.*, **72**, 816 (1950).

lysosomes and the higher endocytic activity of tumor cells.[275] The coupling of dextran with daunomycin,[276,277] methotrexate,[278] and mitomycin C[279] has been reported. The hypoglycemic action of an insulin–dextran conjugate is claimed to be superior and more prolonged than that of insulin itself.[280,281] Coupling of ragweed pollen Antigen A to dextran has been found to reduce the allergenicity and antigenicity of the allergen.[282] Dextran conjugates of anti-inflammatory agents have been studied.[283,284]

Dextran Derivatives

Dextran sulfate Between 1977 and 1989, about 1000 references to dextran sulfates appeared. The biological properties of dextran sulfate continue to provide a fertile area of research. The reports may be grouped according to the following biological effects: enzyme inhibition, activation, or release; effects on immune response; cellular interactions and responses; effects on virus infectivity. Of particular interest, dextran sulfate accelerates hybridization of DNA fragments,[285–287] accelerates transfer of DNA fragments from agarose gels,[287] and is useful for detection of recombinant mammalian viruses in plaques.[288] These anionic derivatives have also proved useful in studying the permeability of biological membranes.[289,290]

DEAE Dextran Reaction of diethylaminoethyl chloride with dextran in alkali affords a derivative in which three kinds of charged amino groups can be distinguished:[213,291] the single DEAE substituent with pK_a 9.2, the tertiary group with pK_a 5.5, and the quaternary group with $pK_a \sim 14$. DEAE-dextrans appear to enhance cellular uptake of viral RNA and intact virus particles[292–295] and the production of interferon by polyribonucleotide complexes.[296–298] These processes appear to operate without detrimental effects on the viability of the cells.[294] Reports on the effects of DEAE-dextrans on tumor growth are contradictory.[299–301]

Fluorescein-Labeled Dextrans Fluorescein isothiocyanate reacts with dextran fractions to give fluorescent derivatives that have proved valuable as macromolecular tracers in studies of microcirculation and vascular permeability in health and disease.[302–308]

Microcarriers for Cell Culture

DEAE-Sephadex can be used as a microcarrier for culturing anchorage-dependent animal cells.[309] Subsequent work has established the optimal degree of substitution for cell growth at about 1.5 meq/g.[310–313]

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been tested as
the leg, pelvi
pertechnate is
dextran to yiel

1. I. W. Sutherla
2. A. Miyazaki,
163374 (1979)
3. A. Jeanes. Am
Publication 13
4. G. J. Walker, I.
5. R. M. Alsop, P.
6. A. Jeanes. Am.
7. A. D. Virnik, K
8. M. Yalpini, CRC
9. A. Jeanes. Mol
10. J. F. Robyt, "E
John Wiley and
11. T. Gospodarek
(1985).
12. A. N. de Belde
sellschaft, Wein
13. M. W. K. Beijer
14. E. J. Hehre. J.
15. E. J. Hehre. Sci
16. K. H. Ebert and
17. J. F. Robyt and
18. A. W. Miller an
19. A. W. Miller an
20. A. W. Miller. S.
21. M. Kobayashi, K
22. P. Monsan, F. P
23. M. Kobayashi an
24. I. Yokoyama, M.
25. G. L. Côté and J
26. S. Huang, H. C.
27. M. M. McCabe.
78, 273 (1977).
28. T. P. Binder, G.
29. K. Itaya and T.
30. W. R. Scales, L.
31. W. Brock Neely
32. J. F. Robyt and

polymerization) 80.[35] Of course, the so-called waxy-type starches that contain no amylose form much more stable pastes.

Derivatization is generally done on a 40–45% suspension of starch in water under alkaline conditions (pH 7–12) at temperatures up to 60°. Because alkalinity is required, salt (usually sodium chloride or sodium sulfate) at a concentration of 10–30% is added to prevent gelatinization. The starch derivative is recovered in granular form by centrifugation or filtration, washing, and drying. Because the gelatinization temperature of the starch decreases as the DS[d] increases, there is a limit to the level of substitution that can be made in aqueous suspension. For this reason, and because a small amount of derivatization often has a dramatic effect on physical properties, the degree of substitution (DS) of most commercial starch derivatives generally falls in the range 0.001–0.2, although some crosslinked derivatives may have an even lower DS and other derivatives may have a DS as high as 0.4.

Ethers

Commercial starch ethers are the hydroxyethyl ether, the hydroxypropyl ether, and cationic ethers.

Hydroxyethylstarch[36–41] Hydroxyethylstarches, made by reaction of slurried starch with ethylene oxide, are used primarily in paper manufacture.[37,42] They are used as a binder for pigmented coatings and as a surface size and are sometimes erroneously called "ethylated" and "ethoxylated" starches. For this use, the starch is usually depolymerized somewhat ("thinned"); to accomplish this depolymerization the starch is acid-modified or thermally coverted in the granular state by the manufacturer or treated with an enzyme such as alpha-amylase or an oxidant such as ammonium persulfate after cooking, that is, in a pasted form by the user (see subsection titled *Depolymerized Starches*). Some hydroxyethylstarches are used as a wet-end additive.

Corn starch and potato starch are the most often used starches in these applications. The molar substitution (MS)[e] of commercial derivatives is generally in or near the range 0.05–0.10. Derivatization of corn starch with hydroxyethyl groups or hydroxypropyl groups in this range markedly alters the properties of the starch. The gelatinization temperature is lowered 5–18°, and the resulting pastes are translucent, very cohesive, and stable, that is, the starch exhibits a much reduced ten-

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[d] DS = degree of substitution (Chapters 18, 20).

[e] MS = moles of substitution (Chapters 19, 20).

Exhibit 10

dency to retrograde. The paste can be cast into relatively clear, flexible, nontacky, water-soluble films.

Hydroxypropylstarch[36–38,43] Hydroxypropylstarches, made by reaction of slurried starch with propylene oxide, are used primarily as food starches.[44–47] They may be purchased either in granular form or as pregelatinized products. They are prepared from waxy maize, corn, potato, and tapioca starches. They are usually also crosslinked (see subsections titled *Starch phosphates* and *Oxidized starches*) to obtain the desired texture and resistance to the high temperatures, low pH values, and shear conditions often encountered in food processing. "Food Starch Modified" is used as a thickener for both water- and milk-based products to provide viscosity stability, to provide water holding, and to increase freeze–thaw stability.

Cationic starch[36,37,40,48] Commercial cationic starches are starch ethers wherein the substituent group (most often) contains a tertiary amino or quaternary ammonium group. The most widely used cationic starches are based upon corn and potato starches. The primary use is as a wet-end additive in paper manufacture.[37,42] The affinity of cationic starch for the negatively charged cellulose fibers, mineral fillers, and pigments results in almost complete adsorption of the starch and produces an adhesive bridge between the components. Some cationic starch is also used as a surface size for paper; for this use, the starch is usually thinned (see subsection titled *Depolymerized Starches*). Cationic starches are also used to flocculate suspensions of negatively charged organic or inorganic particles.

Sulfonium starch derivatives are also known. Also used are amphoteric starches that have a phosphate monoester group in addition to the cationic group.

Esters

The major commercial starch esters are the acetate and phosphate esters. Lesser amounts of the esters of dicarboxylic acids are produced.

Starch acetate[36,49] Starch acetates are used in both food and nonfood applications. They are generally granular, made by reaction of starch in an aqueous slurry (pH 7–8) with acetic anhydride, and generally have a DS below 0.2. Corn, waxy maize, potato, tapioca, sorghum, waxy sorghum, and wheat starches are all converted into acetylated derivatives. Acetylation is often combined with crosslinking or depolymerization via treatment with an acid or an oxidant.

Starches are acetylated to improve the characteristics of their pastes, primarily to retard retrogradation. Starch acetates are used for surface